Author's response to reviews

Title: A patient presenting breast cancer with an unusual paraneoplastic syndrome: a case report

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Author's response to reviews: see over
Dear Editor

Thank you very much for your email dated October 16th. I hereby enclose a revised version of the manuscript as well as full detailed replies to our two reviewers. All the reviewers’ remarks that they have kindly raised were fully addressed “point-by-point” in full details in my accompanying reply. The replies might seem somewhat long; this is because many of the main points raised did include sub-points, which had to be fully addressed. Accordingly, you will find that all relevant points were fully incorporated in the revised version of the manuscript, while those points which were not applicable were still fully addressed in our replies. The revised manuscript is somewhat longer in consequence of the changes proposed by the reviewers.

Once more, on behalf of all the authors we would like to express our deepest gratitude for your great help and support.

Best regards
Joana Silvestre
Reviewer: Eroboghene Ubogu

Dr Eroboghene Ubogu,

First of all, on behalf of the authors, I would like to express gratitude for your suggestions and I agree with you about grammatical errors and structure of the document. An extensive revision of the manuscript has been made. All remarks were fully addressed “point-by-point” in full details in my accompanying reply:

**Title and abstract:**

**First point:** I agree with the reviewer about the title; more emphasis has been given to the title. Changes in the title were made accordingly.

**Second point:** I agree with the reviewer about excluding the race and origin of the patient in this case report, since they do not contribute to the disease. Changes in the text were made accordingly.

**Third point:** Muscle strength was graded according to the Medical Research Council Scale and we have changed the manuscript according to the reviewer suggestions.

**Fourth point:** Electromyogram demonstrated a poor interference pattern during voluntary contraction in several muscles. The pattern has been described in the new manuscript. Changes in the text were made accordingly.

**Fifth point:** Muscle biopsy presented a muscle necrosis pattern, with increased centrally placed nuclei consisting of 3% of total fibers, and substantial numbers of scattered necrotic and regenerating fibers without inflammatory cells. A diffuse replacement of the muscle tissue by adipose and conjunctive tissue was also encountered. Changes in the text were made accordingly. Additional stainings of muscle biopsy are provided.
**Introduction:** Grammatical errors have been corrected.

**Case Presentation:** Grammatical errors and non-standard medical terminology have been corrected.

**First point:** Once again, I agree with the reviewer about excluding the race and origin of the patient in this case report, since they do not contribute to the disease. Changes in the text were made accordingly.

**Second point:** The patient did not present any past history of toxic exposure. These have been mentioned in the new version of the manuscript.

**Third point:** Muscle strength was graded according to the Medical Research Council Scale and we have changed the manuscript according to the reviewer suggestions.

**Fourth point:** I partially agree with the reviewer, since docetaxel, in some patients, has been implicated in some severe sensorimotor neuropathy (Fazio, Acta Neuropathol, 1999. 98(6): 651).

**Fifth point:** The first electromyogram (EMG) performed showed a poor interference pattern during voluntary contraction in the ilioptos and quadriceps femoris. The motor nerve conduction was 44.1 m/s and 44.3 m/s in the right and left tibial nerve respectively, and 46.5 m/s and 46.1 m/s in the right and left peroneal nerve respectively. The second EMG showed the same poor interference during voluntary contraction in bilateral deltoideus, biceps brachii, triceps brachii, ilioptos and quadriceps femoris. The motor nerve conduction velocity was: 44.4 and 45 m/s in right and left median nerves, 49.5 and 48.7 m/s in right and left ulnar nerves, and 39.6 and 40.3 m/s in right and left peroneal nerves. The muscle biopsies have been performed one week after the EMG. The first biopsy has been made on the left quadriceps femoris and the second in the left biceps brachii muscle. These issues have been described in the new version of the manuscript.

**Sixth point:** Figure legends have been revised. New staining with alkaline
phosphatase has been provided. Complement staining was not presented because it is not available in our institution.

**Seventh point:** The viral serologies tested were: serological markers for Hepatitis B, C, Human Immunodeficiency and Human T-Lymphotropic Virus. These have been described in the new version of the manuscript.

**Eight point:** In our institution, prophylaxis to gastrointestinal adverse effects is performed in all patients that receive high doses of steroids. Osteoporotic prophylaxis in this patient has not been done due to the aggressiveness of the underlying disease and due to the low possibility of developing osteoporosis in the future. The patient always tolerated well all chemotherapy and corticotherapy. No steroid sparing agents were used and no side–effects have been described. The improvements in muscle strength started on the second week of therapy, with the patient regaining the ability to walk. There was also a normalization of the muscle enzyme levels. Relapses were observed with the steroid doses of 1,5 mg/kg/day; once she started 3 mg/kg/day of steroids no relapses have been observed. Changes have been described in the new version of the manuscript.

**Discussion:**

**First Point:** Muscle biopsy presented a muscle necrosis pattern, increased centrally placed nuclei consisting of 3% of total fibers, and substantial numbers of scattered necrotic and regenerating fibers without inflammatory cells. A diffuse replacement of the muscle tissue by adipose and conjunctive tissue was also encountered. Changes in the text were made accordingly. Additional stainings of muscle biopsy were provided. I partially agree with the reviewer, since docetaxel, in some patients, has been implicated in some severe sensorimotor neuropathy (Fazio, Acta Neuropathol, 1999. 98(6): 651). Changes in the text were made accordingly.

**Second point:** The aggressiveness of the underlying neoplastic disease is demonstrated through the difficult response to antineoplastic therapy. This could justify the difficulty in improving neurological symptoms since the patient had several relapses. Paraneoplastic syndromes differ widely from individual to individual;
prognosis may vary greatly according to the clinical and immunological features. Two groups of disorders have been considered: one group includes disorders mediated by antibodies against cell surface neuronal antigens (these syndromes often respond to treatment and have a favourable outcome), and another group includes disorders mediated by T-cell mechanisms, that respond poorly to treatment, and have a less favourable outcome (Gatti, Breast, 2003. 12(3): p. 203-7; Gallego, Neurologia, 2008. 23(7): p. 441-8) Changes in the text were made accordingly.

**Conclusions:** Necrotizing paraneoplastic myopathy could be associated to worst prognosis. Levin et al described in their series a 50% of mortality associated to this paraneoplastic syndrome. Some humoral T-cell mechanisms could be responsible for a less favourable outcome. The patient died one year later with pulmonary and hepatic failure due to metastasization of the underlying cancer.
Reviewer: Peter Sillevi Smitt

Dr. Peter Sillevi Smitt,

First of all on behalf of the authors I would like to express gratitude for your suggestions and I agree with you about grammatical errors and structure of the document so extensive revisions have been made. All remarks were fully addressed “point-by-point” in full details in my accompanying reply:

**Major Comments:**
New stainings with alkaline phosphatase have been provided in the new manuscript version. Complement staining was not presented because it is not available in our institution.

**Case presentation:**

**First point:** I agree with the reviewer about excluding the race and origin of the patient in this case report, since they do not contribute to the disease. Changes in the text were made accordingly.

**Second point:** I partially agree with the reviewer, since docetaxel, in some patients, has been implicated in severe sensorimotor neuropathy [Fazio, Acta Neuropathol, 1999. 98(6): 651-3.1].

**Third point:** Muscle strength was graded according to the Medical Research Council Scale and we have changed the manuscript according to the reviewer suggestions.

**Fourth point:** Four months later a new decrease on muscle strength was observed, and the patient noticed difficulty on standing up and in holding her arms. Muscle strength was graded according to MRC as 3 out of 5 in bilateral deltoideus, biceps brachii, and triceps brachii, and 2 out of 5 in the bilateral iliopsoas and quadriceps femoris. Distal strength was preserved. The muscles innervated by cranial nerves were still spared. Changes in the text were made accordingly.
Fifth point: The first electromyogram (EMG) performed showed a poor interference pattern during voluntary contraction in the iliopsoas and quadriceps femoris. The motor nerve conduction was 44.1 m/s and 44.3 m/s in the right and left tibial nerve respectively, and 46.5 m/s and 46.1 m/s in the right and left peroneal nerve respectively. The second EMG showed the same poor interference during voluntary contraction in bilateral deltoideus, biceps brachii, triceps brachii, iliopsoas and quadriceps femoris. The motor nerve conduction velocity was: 44.4 and 45 m/s in right and left median nerves, 49.5 and 48.7 m/s in right and left ulnar nerves, and 39.6 and 40.3 m/s in right and left peroneal nerves. The muscle biopsies have been performed one week after the EMG. The first biopsy has been made on the left quadriceps femoris and the second on the left biceps brachii muscle. These questions have been described in the new version of the manuscript.

Sixth point: The patient had been given the maximum allowable dose of cyclophosphamide, methotrexate and 5-fluoruracil, and had still not completed the full dose of epirubicin and docetaxel. Since the disease was still progressing, the oncologist believed that the chemotherapy needed to be consolidated. Nevertheless, I agree that that is a debatable issue.